REMARKS

In this Request for Continued Examination, claims 1 and 17 have been amended to more particularly point out and distinctly claim the invention. Particularly an aspect of the invention related to weighing the bioreactor to determine how much additional medium is necessary, followed by control of the feed pumps necessary to introduce additional medium into the bioreactor has been added to claims 1 and 17. Additionally the regulator and reference operator connected to the sensor for measuring cell concentration have been renamed as the "first regulator (42)" and "first reference operator (43)" in order to distinguish them from the "second regulator (44)" and "second reference operator (45)". Applicants acknowledge that these elements in the specification are referred to as the second and third of each respective element as opposed to the first and second, however, since the first regulator and first reference operator as defined by the specification are not recited in claims 1 or 17, Applicants have changed the names to keep the claim language understandable (the reference numbers which more specifically define each element have remained the same as the specification definitions). Support for these amendments can be found in the specification as originally filed at paragraphs 0043-0044 of the published application and in Figures 1 and 3. No new matter has been added. Further, claims 20 and 21 have been cancelled.

In paragraphs 2-19 of the Office Action the Examiner rejected claims 1-16 under 35 U.S.C. §103(a) as being obvious over CAB8-Computer Applications in Biotechnology, June 25-27, 2001 (hereinafter "Cornelissen") in view of Biotechnology and Bioengineering, vol. 34, pp 592-599 (1989) (hereinafter Major), and U.S. Published Application No. 2002/0138454 A1 (hereinafter Gruenberg), and further in view of United States Patent No. 6,402,941 (hereinafter Lucido).

Reconsideration is requested.

Claim 1 recites a novel method for biotechnologically producing valuable products using a system of feed receptacles, a bioreactor, pumps, a cross flow filtration unit and at least two harvest receptacles, one for storing filtered permeate and a second for storing concentrated retentate. Claim 1 further recites that the method measures the cell concentration of the bioreactor by use of the control unit (6), an analytical system (27), a sensor (28) for measuring cell concentration, an analyzer (41), a first regulator

(42), and a first reference operator (43), and then adjusts the cell concentration to a predetermined level by moving cells from the bioreactor (1) to the second harvest receptacle (18) through the use of a harvest pump (20). Claim 1 as presently amended further recites a second regulator (44) which receives a signal from a weighing device (22) which measures the weight of the bioreactor (1), and wherein said second regulator (44) compares the weight of said bioreactor (1) with a desired weight stored in a second reference operator (45), and based on the comparison of the measured weight and the desired weight said second regulator sends a control signal to an upstream feed pump (8), which in turn sends medium to the bioreactor (1) from an upstream medium containing feed receptacle (2).

The added subject matter relating to the weighing of the bioreactor followed by addition of medium from an upstream feed receptacle via an upstream feed pump was partially contained in original claim 21. The Examiner had stated that original claim 21 was rendered obvious by the disclosure in Cornelissen of a weighing device connected to the bioreactor shown in Figure 3 of Cornelissen. Applicants submit that the disclosure in Cornelissen does not teach the elements currently recited in claim 1. Specifically the weighing device in Cornelissen is connected to a pump on the downstream side of the bioreactor, wherein the downstream pump connects a product harvest receptacle and a microfiltration device, both of which are also on the downstream side of the bioreactor. This disclosure teaches away from the presently claimed invention where the weighing device is connected to an upstream feed pump connected to an upstream medium containing feed receptacle.

The Examiner has stated in paragraph 6 of the Office Action that the primary reference, Cornelissen does not teach a second harvest vessel. The Examiner has also stated in paragraph 9 of the Office Action that Cornelissen does not disclose a method for measuring the cell concentration in the bioreactor. Applicants submit that the Examiner is correct in highlighting these deficiencies in the primary reference and further submit that neither Cornelissen, nor the secondary references, disclose or suggest the recited method, including each and every element used to measure the cell concentration and then readjust the cell concentration in the bioreactor to the desired level. Further, the cited art does not disclose a weighting device for the bioreactor connected to an upstream feed pump connected to an upstream medium containing feed receptacle.

To alleviate the deficiencies in Cornelissen, the Examiner has cited three additional documents. The first reference is Major, which discloses a continuous fermenter for producing lactate. The only disclosure in the journal article cited by the Examiner is a simple figure on page 593, and one paragraph on page 594, which briefly describes the re-circulation process used in Major. The description in Major of a recycling system does not render obvious the system disclosed in the Claim 1 of the present invention because there is no instruction or need described in Major to use a more complicated cell growing system as taught in the present invention, nor is there an instruction in Cornelissen to use a recycling system as taught in Major. Moreover, neither reference discloses or suggests the need to measure cell concentration, a system for cell concentration measurement or a system for readjusting cell concentration. Additionally, neither Major nor Cornelissen teach the use a regulator connected to a device for weighing the bioreactor, wherein the regulator is further connected to a reference operator to compare the measured weight with the reference weight, and wherein the regulator is further connected to an upstream feed pump which in turn is connected to an upstream feed receptacle, which can supply medium to replenish the bioreactor.

Next the Examiner points to Gruenberg and Lucido in an attempt to alleviate the deficiency in Cornelissen and Major, namely, the lack of instruction regarding the method for measuring and controlling the cell concentration in the bioreactor. As disclosed above, claim 1 recites a method for measuring cell concentration of the bioreactor using a control unit (6), an analytical system (27), a sensor (28) for measuring cell concentration, an analyzer (41), a first regulator (42), and a first reference operator (43), wherein the cell concentration is removed from the bioreactor (1) to the second harvest receptacle (18) through the use of a harvest pump (20). None of these claim elements are disclosed in the cited prior art in the combination recited in claim 1.

While Gruenberg teaches a device for measuring the weight of the nutrient feed or the weight of the bioreactor, it does not teach a method of measuring the cell concentration in the bioreactor and a method for regulating the cell concentration of the bioreactor. Gruenberg teaches the use of a Mettler balance in combination with a peristaltic pump and a software solution which may be connected with the bioreactor or to nutrient medium containers. *See* Paragraphs 0060, 0109 and 0121. However, these

elements are not equivalent to the control unit (6), an analytical system (27), sensor (28) for measuring cell concentration, analyzer (41), first regulator (42), and first reference operator (43) as recited in claim 1. Further, since the elements disclosed in Gruenberg, relate to a method for measuring nutrient feed or reactor weight, they have no relation to the specific measuring and removing of cell concentration recited in claim 1. *See* Gruenberg at paragraphs 0019, 0064, 0109, 0121-0122. Therefore each and every element of claim 1 is not disclosed or suggested by the cited prior art.

Applicants acknowledge that Gruenberg teaches the use of a Mettler balance in combination with a peristaltic pump and a software solution. *See* Paragraphs 0060-0064, 0109 and 0121-0122. However, there is no instruction or suggestion to arrange these elements in the specific configuration as recited in the present claims. Moreover, Gruenberg teaches in paragraph 0060 that the Mettler balance is connected to a hardware controller that sends a signal to a discharge pump of the bioreactor. *See id.* Therefore the teaching in Gruenberg is to control the feed concentration by reducing the volume of the bioreactor. This is not the teaching recited in the present claims which recite that the second regulator (44) is connected to a feed pump (8) (not a discharge pump) on the upstream side of the bioreactor. Additionally, in paragraphs 0062-0064, and Table 1, Gruenberg teaches that Mettler balances can be connected to the nutrient feed containers to measure the amount of nutrient feed. This is not a teaching to control the amount of nutrient feed in the bioreactor based on the weight measurement of the bioreactor, and especially not a teaching to use a regulator connected to a reference operator, and an upstream feed pump to control the feed concentration in a bioreactor.

The additional teachings in paragraphs 0109 and 0121-0122 of Gruenberg in relation to the control of the nutrient feed do not contradict the teachings of paragraphs 0060-0064. While paragraphs 0121-0122 recite "a device for measuring and controlling the amount of the nutrient medium mixture introduced into the bioreactor" and the use of a balance, software and peristaltic pump, it does not specifically recite the specific combination of a second regulator (44), which is connected to the following three claim elements: (I) a weighing device (22) connected to the bioreactor; (II) a second reference operator (45) which contains stored weight values for the bioreactor; and (III) an upstream feed pump (8) which is in turn connected to an upstream medium containing feed receptacle (2). Specifically, the teaching in Gruenberg never discloses that the

device for measuring the weight of the bioreactor is directly connected to anything but a discharge pump (not a feed pump) and that while the nutrient feed receptacles are connected to a balance, software and pumps, they are not directly connected to a device for measuring the weight of the bioreactor.

Lucido discloses an apparatus for biological treatment of environmental contaminants and waste. The teachings highlighted by the Examiner in Lucido are contained in col. 8, lines 30-35, which teach that an optical sensor can be used to measure turbidity in the bioreactors, and that a higher turbidity can indicate a higher viable cell concentration. *See id.* Applicants submit that the above teaching does not render obvious the recited claim elements in claim 1, namely, a control unit (6), an analytical system (27), a sensor (28) for measuring cell concentration, an analyzer (41), a first regulator (42), and a first reference operator (43), wherein the cell concentration is removed from the bioreactor (1) to the second harvest receptacle (18) through the use of a harvest pump (20). There is not even a process disclosed in Lucido to alter the cell concentration in the bioreactor, only a process that recites an "alarm is hooked up to a computer via telephone lines which relays the sounding of the alarm to a central station. At this station the problem can be assessed and a repair unit dispatched as needed". *See* Lucido at Col. 8, lines 36-40. This process cannot be compared to the fully automated system for measuring and controlling cell concentration in the bioreactor as recited in claim 1 of the present invention. Furthermore, because Lucido is related to a process for removing industrial waste from sewage systems, Applicants submit that this is non-analogous art, and therefore would not be used by a person skilled in the art looking to add to the teachings of Major, Cornelissen and/or Gruenberg.

The remaining dependent claims 2-16 all incorporate each and every limitation of claim 1, and therefore are also not rendered obvious by the cited prior art.

With regard to the Examiner's statements in the Response to Arguments section of the June 8, 2009 Office Action at page 12, Applicants submit that the Examiner is improperly using hindsight based on the present specification to reconstruct the claimed invention. Further, the Examiner has provided no motivation or suggestion to combine the cited art. Specifically, the statement "the skilled artisan would be fully capable of and would find it obvious to modify the software to process the incoming data signal and send a response to the harvest pump via the process computer based on a programmed

reference or set-point" contains at least four assumption for which the Examiner has provided no support. There is no specific teaching in Lucido or anywhere else in the prior art related to directly measuring cell concentration in a bioreactor as recited in the present claims, and the Examiner's hindsight analysis coupled with multiple assumption creates an improper 35 U.S.C. §103(a) rejection.

Further, as discussed above, the teachings in Gruenberg at best relate to the measurement of feed medium or the weighing of the bioreactor, not to the individual measurement of cell concentration in the bioreactor, and therefore the Examiner is making additional assumptions about a system for controlling and measuring cell concentration, where no such system has been shown to exist in the cited prior art. Further, as discussed above, the teaching in Gruenberg are more closely related to a system for measuring nutrient medium or the weight of a bioreactor, and therefore provide no teaching or suggestion for a system for measuring and controlling cell concentration.

Therefore because the cited prior art does not teach or suggest each and every element of claims 1-16, it is requested that the above §103(a) rejection be withdrawn.

In paragraphs 20-24 of the Office Action the Examiner rejected claims 17-19 and 21 under 35 U.S.C. §103(a) as being obvious over Cornelissen in view of Major and Gruenberg.

Reconsideration is requested.

Claim 17 has been amended to contain the subject matter of former claim 21 and additional elements recited in paragraph 0044 of the published application. In addition to the claim elements related to the measurement of cell concentration described above, which are not contained in the cited prior art, claim 17 currently further recite a second regulator (44) which receives a signal from a weighing device (22) which measures the weight of the bioreactor (1), and that said second regulator (44) is connected to a second reference operator (45) which contains stored weight measurements, and wherein said second regulator is further connected to an upstream feed pump (8), which is connected to an upstream medium containing feed receptacle (2), which is capable of sending medium to the bioreactor. The Examiner had stated that original claim 21 was rendered obvious by the disclosure in Cornelissen of a weighing device connected to the bioreactor shown in Figure 3 of Cornelissen. Applicants submit that the disclosure in Cornelissen

does not teach the elements currently recited in claim 17. Specifically the weighing device in Cornelissen is connected to a pump on the downstream side of the bioreactor, wherein this downstream pump connects a product harvest receptacle and a microfiltration device, both of which are also on the downstream side of the bioreactor. This disclosure teaches away from the presently claimed invention where the weighing device is connected to an upstream feed pump connected to an upstream medium containing feed receptacle.

Additionally as discussed, the cited prior art, namely, Cornelissen, Major and Gruenberg (and even Lucido, which has not been included in this rejection), does not teach or suggest each and every element of claim 17 of the present application. Specifically, the cited prior art does not teach the elements for measuring cell concentration in a bioreactor and the elements necessary for removing excess cell concentration from said bioreactor as recited in claim 17. Additionally, as discussed above, the cited art does not teach or suggest the specific second regulator (44), which is connected to the following three claim elements: (I) a weighing device (22) connected to the bioreactor; (II) a second reference operator (45) which contains stored weight values for the bioreactor; and (III) an upstream feed pump (8) which is in turn connected to an upstream medium containing feed receptacle (2).

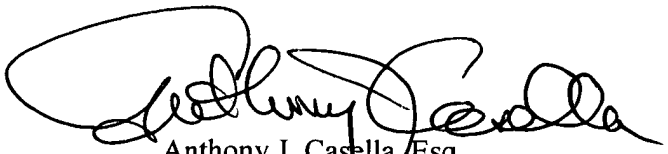
With regard to the Examiner's statement in the June 8, 2009 Office Action on pages 12-13, that Applicants are simply restating arguments related to method claims for apparatus claims, Applicants submit that the restatement of arguments is solely related to the existence of each and every apparatus claim element recited in claim 17, which also appear in claim 1, and the Examiner has not attempted to refute the Applicants arguments, especially in relation to the existence of a system for measuring and controlling cell concentration in the bioreactor.

Therefore, it is requested that the §103(a) rejection with regard to claims 17-19 be withdrawn.

Based upon the above amendments and remarks, Applicants respectfully submit that claims 1-19 are allowable over the prior art and that the present application is in proper form for allowance.

Favorable consideration and early allowance is respectfully requested and earnestly solicited.

Respectfully submitted,



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